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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/472,558	12/27/1999	MOHAMMAD B. BAHRAMIAN	2281/102	8925
2101	7590	11/10/2003	EXAMINER	
BROMBERG & SUNSTEIN LLP 125 SUMMER STREET BOSTON, MA 02110-1618			PARAS JR, PETER	
			ART UNIT	PAPER NUMBER
			1632	

DATE MAILED: 11/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/472,558	BAHRAMIAN ET AL.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 8/7/03; 8/19/03; 8/26/03.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 11, 14, 28-49, 51, 53-60 and 69-84 is/are pending in the application.
- 4a) Of the above claim(s) 28-49, 51 and 53-56 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 11, 14, 57-60 and 69-84 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☒ Interview Summary (PTO-413) Paper No(s). 1103.
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

Applicant's amendments received on 8/7/03, 8/19/03, and 8/26/03 have been entered. Claims 11, 14, 57, 60, and 69 have been amended. Claims 12-13, 15-24 and 61-68 have been cancelled. New claims 70-84 have been added. Claims 11, 14, 28-49, 51, 53-60 and 69-84 are pending. Claims 11, 14, 57-60, and 69-84 are under current consideration.

Election/Restrictions

Claims 28-49, 51 and 53-56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 5.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Claim Objections

Claim 80 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 60. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is

proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112, 1st paragraph

New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 70-79 and 81-83 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

The claims embrace co-transfection of muting nucleic acid sequences, wherein a first muting nucleic acid sequence mutes at the level of post-transcription and a second muting nucleic acid sequence mutes at the level of transcription.

The specification provides no implicit or explicit support for the context of the muting expression of an endogenous gene, wherein muting results from co-introduction of separate muting nucleic acid sequences, a first muting nucleic acid sequence and a second muting nucleic acid sequence, and wherein the first nucleic acid sequence

mutates at the level of post-transcription and the second nucleic acid sequence mutates at the level of transcription. The specification has only provided support for muting expression of an endogenous gene at the level of transcription and post-transcription in the context of introduction of a single muting nucleic acid sequence that is capable of muting at both the level of transcription and post-transcription. See page 14 of the specification, which describes muting at the level of transcription and post-transcription by introduction of a DNA single sequence, the sequence of the $\alpha 1(I)$ procollagen gene, present in pWTC. Patentees cannot pick characteristic possessed by two of their formulations and then make it basis of claims that cover any formulation having that characteristic. See *Purdue Pharma L.P. v. Faulding Inc.*, 56 USPQ2D 1481 (CA FC 2000). Applicants are reminded that it is their burden to show where the specification supports any amendments to the claims. See 37 CFR 1.121 (b)(2)(iii), the MPEP 714.02, 3rd paragraph, last sentence and also the MPEP 2163.07, last sentence.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP

2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. *Applicant should therefore specifically point out the support for any amendments made to the disclosure* [or point to case law supporting incorporation of such a limitation as in the instant case]".

The previous rejections under 112, 1st paragraph are withdrawn in view of the amendments to the claims. The Bahramian declaration was considered to be moot as the previous enablement rejection was withdrawn in light of Applicant's amendments to the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 57-60, 71-76 and 80-84 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 57 and 80 are indefinite as written. The claims embrace muting expression of an endogenous gene in cultured animal cells, particularly rodent cells, wherein the gene is a tat gene. The claims are indefinite because the tat gene is a viral

gene, particularly an HIV gene, and is not considered to be a gene endogenous to animal cells. Claims 58-60 and 71-76 depend from claim 57 and claims 81-84 depend from claim 80.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 11, 14, 57, 60 and 80 are rejected under 35 U.S.C. 102(e) as being anticipated by Fire et al (6,506,559).

The claims are directed to methods of muting expression of an endogenous gene in a cultured population of animal cells, particularly rodent cells, the method comprising screening to identify a muting nucleic acid composition that is homologous to a sequence in the endogenous gene, wherein the nucleic acid sequence is double-stranded, identifying a first sequence of a muting nucleic acid sequence, delivering said first muting nucleic acid sequence to the population of cells, and muting expression of the endogenous gene at the level of post-transcription.

Fire et al teach methods of inhibiting expression of a target gene within a cell comprising identifying and delivering inhibitory RNA, which can be delivered in the form of RNA or DNA (see columns 12-13), homologous to portions of the endogenous gene that mutes at the level of post-transcription (see column 6). Fire et al further teach that the cell may be derived from or contained within any organism (plant, animal, protozoan, virus, bacterium, or fungus). See the paragraph bridging columns 4-5. Fire et al further teach that animal cells can include fish, mammals, such as rodents, as well as invertebrates. See column 8. Fire et al teach that the target gene could be any gene or nucleotide sequence including cytokines/lymphokines. See column 11. Fire et al teach the identification of nucleic acid molecules that inhibit expression of endogenous genes in columns 14-24.

Thus, the teachings of Fire et al meet all of the instant claim limitations.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 57-59 and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al taken with WO 94/11494 (Prockop et al).

The claims are directed to methods of muting expression of an endogenous gene in a cultured population of animal cells, the method comprising screening to identify a muting nucleic acid composition that is homologous to a sequence in the endogenous gene, wherein the nucleic acid sequence is double-stranded, identifying a first sequence of a muting nucleic acid sequence, delivering said first muting nucleic acid sequence to the population of cells, and muting expression of the endogenous gene at the level of post-transcription. The claims are further directed to method of muting expression of an endogenous gene in a population of rodent cells.

Fire et al teach methods of inhibiting expression of a target gene within a cell comprising identifying and delivering inhibitory duplex RNA, which can be delivered in the form of RNA or DNA (see columns 12-13), homologous to portions of the endogenous gene that mutes at the level of post-transcription (see column 6). Fire et al further teach that the cell may be derived from or contained within any organism (plant, animal, protozoan, virus, bacterium, or fungus). See the paragraph bridging columns 4-5. Fire et al further teach that animal cells can include fish, mammals, such as rodents,

as well as invertebrates. See column 8. Fire et al teach that the target gene could be any gene or nucleotide sequence. See column 11. Fire et al teach the identification of nucleic acid molecules that inhibit expression of endogenous genes in columns 14-24. Fire et al discuss that RNA interference has the following advantages over antisense interference: 1) the ability to use a low concentration of a naturally occurring nucleic acid; and 2) the ability to target any gene by using any portion of the target gene's nucleotide sequence. See column 5, in lines 15-30.

Fire et al differs from the instant claimed invention as it does not specifically teach inhibition of expression of a collagen gene.

However, at the time the claimed invention was made, WO 94/11494 taught a method for inhibiting the expression of the human or mouse $\alpha 1(I)$ procollagen gene in rodent cells using antisense sequences. See pages 6-7 and 17. WO 94/11494 discuss that inhibition of expression of procollagen genes can be used to treat diseases related to mutant procollagen genes. See pages 4-6.

Accordingly, it would have been obvious at the time the claimed invention was made, to modify the teachings of WO 94/11494 by use of interfering duplex RNA molecules according to Fire et al. One of ordinary skill in the art would have been sufficiently motivated to make such a modification in light of the teachings of Fire et al, which suggest that use of duplex interfering RNA is more efficient at inhibiting expression of a target gene than antisense molecules and also because it was an art-recognized goal to treat collagen related diseases as discussed by WO 94/11494.

Thus, the claimed invention, as whole, was clearly *prima facie* obvious in the absence of evidence to the contrary.

Allowable Subject Matter

Claims 69 and 77-79 may be allowable if limited to rodent cells *in vitro* and if limited to introduction of a single muting DNA sequence.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Official Fax Center number is (703) 872-9306.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (703) 305-3388.

Peter Paras, Jr.

**PETER PARAS
PATENT EXAMINER**

Art Unit 1632

